Connecting via Winsock to STN

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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS 4	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS 5	FEB 05	German (DE) application and patent publication number format changes
NEWS 6	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS 7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS 8	MAR 03	FRANCEPAT now available on STN
NEWS 9	MAR 29	Pharmaceutical Substances (PS) now available on STN
NEWS 10	MAR 29	WPIFV now available on STN
NEWS 11	MAR 29	New monthly current-awareness alert (SDI) frequency in RAPRA
NEWS 12	APR 26	PROMT: New display field available
NEWS 13	APR 26	IFIPAT/IFIUDB/IFICDB: New super search and display field available
NEWS 14	APR 26	LITALERT now available on STN
NEWS 15	APR 27	NLDB: New search and display fields available
NEWS 16	May 10	PROUSDDR now available on STN
NEWS 17	May 19	PROUSDDR: One FREE connect hour, per account, in both May and June 2004
NEWS 18	May 12	EXTEND option available in structure searching
NEWS 19	May 12	Polymer links for the POLYLINK command completed in REGISTRY
NEWS 20	May 17	FRFULL now available on STN
NEWS 21	May 27	STN User Update to be held June 7 and June 8 at the SLA 2004 Conference
NEWS 22	May 27	New UPM (Update Code Maximum) field for more efficient patent SDIs in CAplus
NEWS 23	May 27	CAplus super roles and document types searchable in REGISTRY
NEWS 24	May 27	Explore APOLLIT with free connect time in June 2004

NEWS EXPRESS	MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:06:02 ON 17 JUN 2004

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.42	0.42

FILE 'REGISTRY' ENTERED AT 13:07:04 ON 17 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 16 JUN 2004 HIGHEST RN 694434-66-7
DICTIONARY FILE UPDATES: 16 JUN 2004 HIGHEST RN 694434-66-7

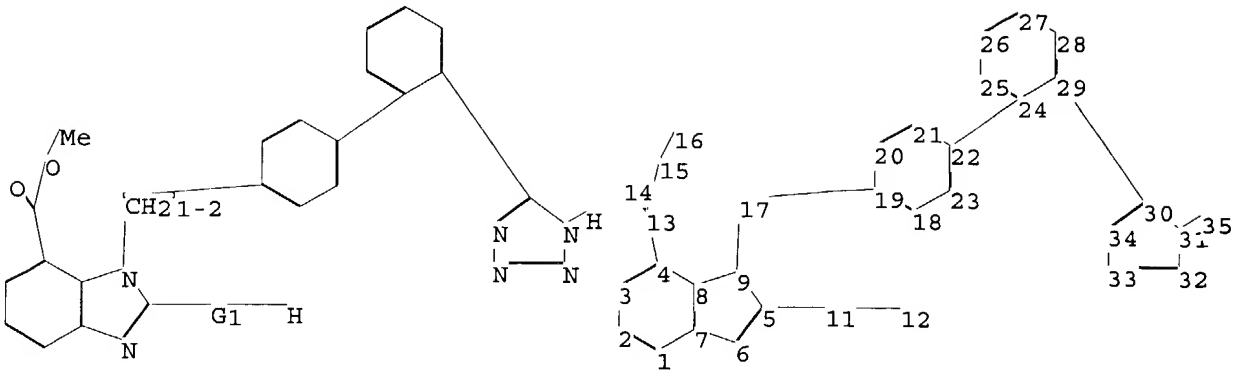
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Program Files\Stnexp\Queries\10612984.str



chain nodes :
11 12 13 14 15 16 17 35
ring nodes :
1 2 3 4 5 6 7 8 9 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
chain bonds :
4-13 5-11 9-17 11-12 13-14 13-15 15-16 17-19 22-24 29-30 31-35
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9 18-19 18-23 19-20 20-21 21-22 22-23 24-25 24-29 25-26 26-27 27-28 28-29 30-31 30-34 31-32 32-33 33-34

exact/norm bonds :
5-6 5-9 5-11 6-7 8-9 11-12 13-14 13-15 30-31 30-34 31-32 32-33 33-34
exact bonds :
4-13 9-17 15-16 17-19 22-24 29-30 31-35
normalized bonds :
1-2 1-7 2-3 3-4 4-8 7-8 18-19 18-23 19-20 20-21 21-22 22-23 24-25 24-29 25-26 26-27 27-28 28-29
isolated ring systems :
containing 1 : 18 : 24 : 30 :

G1:O,S,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom 32:Atom 33:Atom 34:Atom 35:CLASS

L1 STRUCTURE UPLOADED

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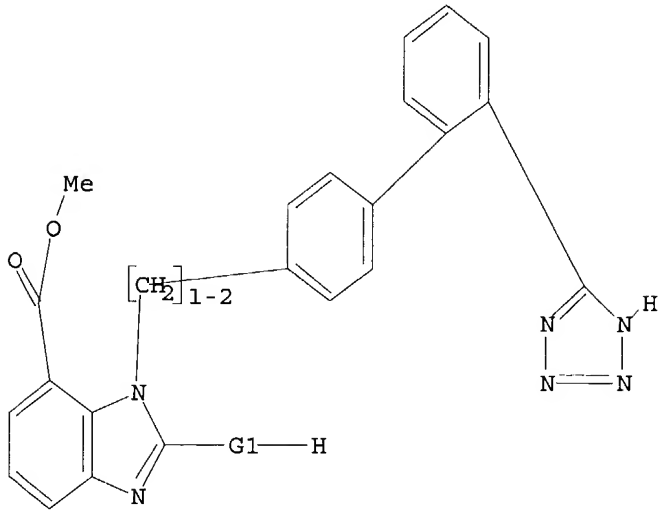
L1 HAS NO ANSWERS
L1 STR



G1 O,S,N

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -      4 TO ITERATE

100.0% PROCESSED       4 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            4 TO      200
PROJECTED ANSWERS:               0 TO        0

L2             0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 13:07:33 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    112 TO ITERATE

100.0% PROCESSED     112 ITERATIONS                               12 ANSWERS
SEARCH TIME: 00.00.01

L3            12 SEA SSS FUL L1

=> FIL CAPLUS
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             155.42     155.84

FILE 'CAPLUS' ENTERED AT 13:07:38 ON 17 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 17 Jun 2004 VOL 140 ISS 25
FILE LAST UPDATED: 16 Jun 2004 (20040616/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 6 L3

=> s l3/p
L5 5 L3/P

=> s l4 and py<=1990
13515463 PY<=1990
L6 0 L4 AND PY<=1990

=> d l6 ibib abs hitstr tot
L6 HAS NO ANSWERS
'IBIB ABS HITSTR ' IS NOT A VALID STRUCTURE FORMAT KEYWORD
Structure Formats
SIA ----- Structure Image, Attributes, and map table if it contains data. (Default)
SIM ----- Structure IMage.
SAT ----- Structure ATtributes and map table if it contains data.
SCT ----- Structure Connection Table and map table if it contains data.
SDA ----- All Structure DAta (image, attributes, connection table and map table if it contains data).
NOS ----- NO Structure data.
ENTER STRUCTURE FORMAT (SIA), SCT, SDA, SIM, SAT, NOS:end

=> d l5 ibib abs hitstr tot

L5 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:133265 CAPLUS
DOCUMENT NUMBER: 138:170242
TITLE: Preparation of crystals of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid and process for producing the same
INVENTOR(S): Hashimoto, Hideo; Maruyama, Hideaki
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003014112	A1	20030220	WO 2002-JP7861	20020801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1420016	A1	20040519	EP 2002-758782	20020801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2003113180	A2	20030418	JP 2002-225642	20020802

PRIORITY APPLN. INFO.: JP 2001-236802 A 20010803
WO 2002-JP7861 W 20020801

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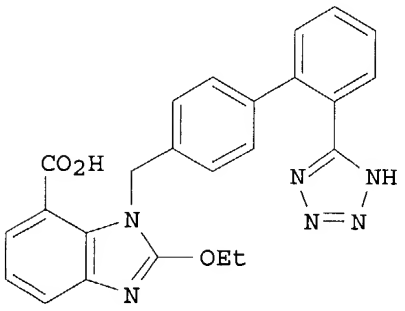


I

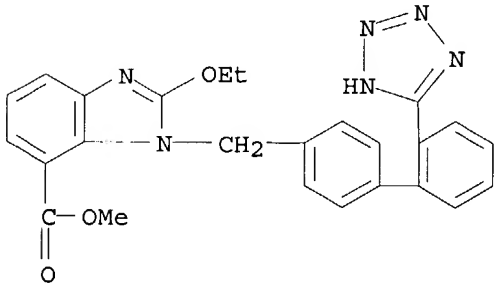
AB Disclosed is a process for producing crystals of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (I), characterized by dissolving or suspending the compound I or a salt thereof in a solvent comprising an aprotic polar solvent and crystallizing it. By the process, the impurities which are contained in the compound I or its salt and are difficult to remove, such as tin compds., analogs of the compound I, and a residual organic solvent, can be easily removed. Crystals of the compound I can be efficiently and easily mass-produced in high yield on an industrial scale. The compound I is useful as an angiotensin II inhibitor for the treatment of diseases induced by angiotensin II or a factor induced by angiotensin II, or diseases induced by angiotensin II receptor-mediated vascular contraction and proliferation and organ disorders, e.g. hypertension and heart diseases. Thus, 5.0 g I (preparation given), 6 mL THF, and 6 mL H2O were mixed, dissolved, stirred with 0.15 g activated charcoal for .apprx.30 min, filtered, followed by washing the charcoal with a mixture of THF and H2O (9:1) (10 mL), and the filtrate and the washing were combined, treated dropwsie with 87.5 mL H2O, and stirred for .apprx.1 h. The precipitated crystals were separated, washed with 20 mL THF/H2O (2:3), and dried to give 4.5 g I (90% yield) containing 0.08% ketone, 0.06% ester, 3,780 ppm THF, and ≤0.6 ppm Sn.

IT **139481-69-9P**, Methyl 1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-

yl)methyl]-2-ethoxybenzimidazole-7-carboxylate
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis to free acid)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:779811 CAPLUS
DOCUMENT NUMBER: 130:53943
TITLE: Production of aminobenzene compounds with improved worker safety
INVENTOR(S): Hashimoto, Hideo; Hanaoka, Tadashi; Kato, Masayasu
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 31 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 881212	A1	19981202	EP 1998-109211	19980520
EP 881212	B1	20011031		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6177587	B1	20010123	US 1998-80456	19980519
AT 207884	E	20011115	AT 1998-109211	19980520
ES 2162367	T3	20011216	ES 1998-109211	19980520
CA 2238427	AA	19981126	CA 1998-2238427	19980525
CN 1203223	A	19981230	CN 1998-101894	19980525
JP 11043474	A2	19990216	JP 1998-142653	19980525
JP 3003030	B2	20000124		

PRIORITY APPLN. INFO.: JP 1997-134195 A 19970526
OTHER SOURCE(S): MARPAT 130:53943
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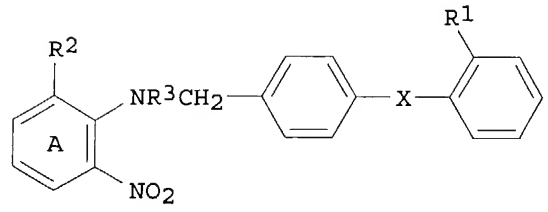
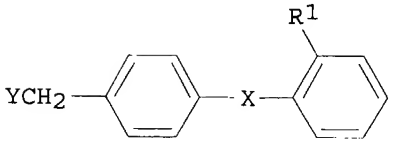


I



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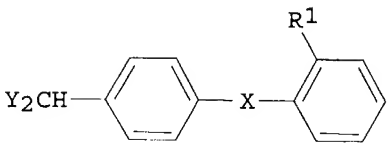

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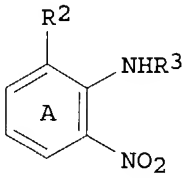


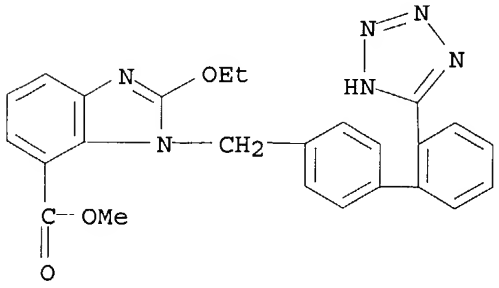
IV

AB Aminobenzene compds. I (R1, R2 are groups capable of forming an anion; R3 = acyl; X = bond, spacer of 1-2 atoms; A is a benzene ring which may have addnl. optional substituents) are prepared by reacting a mixture of a monohalogen compound II (Y is a halogen) and dihalogen compound III with an aminobenzene IV. The I are easily produced in in good yield in a completely airtight system, avoiding worker exposure to mutagenic II and salts thereof, and are useful as synthetic intermediates for the production of medicines.

IT **139481-69-9P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of; in production of aminobenzene compds. with improved worker safety)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:270821 CAPLUS
DOCUMENT NUMBER: 120:270821
TITLE: Tri-higher alkyl tin azide and its use
INVENTOR(S): Kato, Takeshi; Shida, Yasushi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 578125	A1	19940112	EP 1993-110458	19930630
EP 578125	B1	19980401		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5484955	A	19960116	US 1993-83697	19930629
AT 164584	E	19980415	AT 1993-110458	19930630
ES 2113975	T3	19980516	ES 1993-110458	19930630
CA 2099822	AA	19940107	CA 1993-2099822	19930705
CA 2099822	C	20031216		
JP 06073028	A2	19940315	JP 1993-166639	19930706
JP 2990566	B2	19991213		
JP 06073029	A2	19940315	JP 1993-166640	19930706
US 5599943	A	19970204	US 1995-519717	19950828

PRIORITY APPLN. INFO.: JP 1992-178484 A 19920706
US 1993-83697 A3 19930629

OTHER SOURCE(S): MARPAT 120:270821
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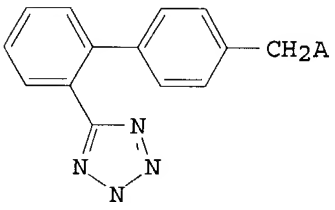

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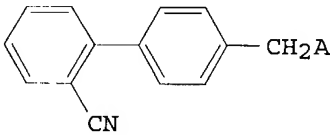
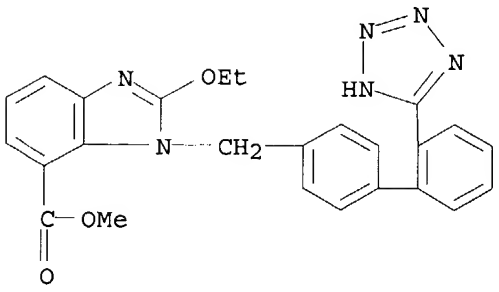


II

AB Disclosed are a compound of the formula (R)3SnN3, wherein R is a C7-18 alkyl, and a process for producing a tetrazolylbenzene compd.of formula I (A = H, phthalimido group) which comprises reacting a cyanobenzene compound, e.g., II with a (R)3SnN3. This process is useful for a safe and com. profitable production of the tetrazolylbenzene compound which is employed for producing a tetrazole derivative having a hypotensive action based on angiotensin II-antagonizing activity or a production intermediate thereof.

IT **139481-69-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 139481-69-9 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:560184 CAPLUS
DOCUMENT NUMBER: 119:160184
TITLE: Nonpeptide angiotensin II receptor antagonists. Synthesis and biological activity of benzimidazolecarboxylic acids
AUTHOR(S): Kubo, Keiji; Kohara, Yasuhisa; Imamiya, Eiko; Sugiura, Yoshihiro; Inada, Yoshiyuki; Furukawa, Yoshiyasu; Nishikawa, Kohei; Naka, Takehiko
CORPORATE SOURCE: Pharm. Res. Div., Takeda Chem. Ind., Ltd., Osaka, 532, Japan
SOURCE: Journal of Medicinal Chemistry (1993), 36(15), 2182-95
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
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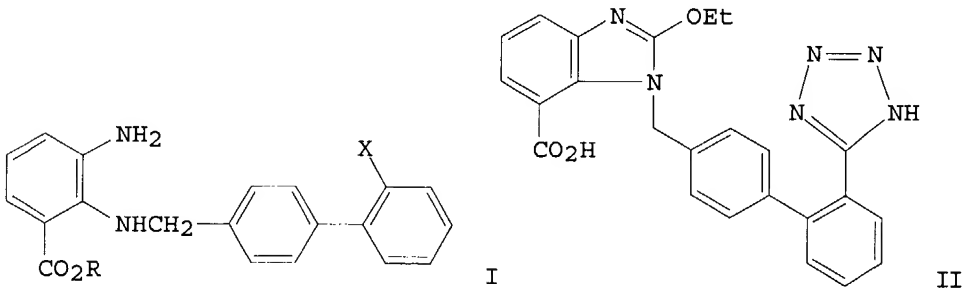


I II

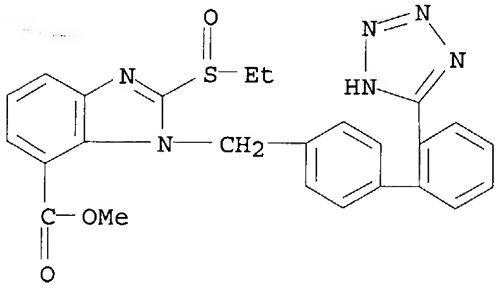
AB A series of 2-substituted-1-(biphenyl-4-ylmethyl)-1H-benzimidazole-7-carboxylic acids was prepared from the key intermediate 3-amino-2-[(biphenyl-4-ylmethyl)amino]benzoate I (R = Me, Et, X = CN, R = Me, X = CO2Me) in order to clarify the structure-activity relationships of various analogs of 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (CV-11194), a potent and long acting angiotensin II (AII) receptor antagonist. The AII antagonistic activity of the benzimidazoles was investigated by in vitro assays, which included an AII receptor binding assay and AII-induced vasocontraction assay, as well as by in vivo assays such as an AII-induced pressor response in rats. Most of the benzimidazoles showed high affinity for the AII receptor (IC50 value, 10-6-10-7 M) and inhibited the AII-induced pressor response at 1 or 3 mg/kg po, and the effects were more potent than those of CV-11194 and DuP753. The structure-activity relationship studies on the binding affinity and the inhibition of AII-induced pressor response suggested that

straight chains of a certain length (e.g., ethoxy groups, Et groups) were the best as substituents at the 2-position and that their steric factors, lipophilicity, and electronic effects affected the potency of the AII antagonistic action. Both a carboxyl group at the 7-position and a tetrazole ring at the 2'-position were particularly important for potent and orally active AII antagonistic activity and a long-acting hypotensive effect. The representative compound, 2-ethoxy-1-[[2-(1H-tetrazol-5-yl)biphenyl]-4-ylmethyl]-1H-benzimidazole-7-carboxylic acid (CV-11974) (II), inhibited the specific binding of [125I]AII to bovine adrenal cortical membrane with an IC50 value of 1.1 + 10-7 M. The AII-induced contraction of rabbit aortic strips was antagonized by CV-11974 (IC50 value, 3.0 + 10-10 M). Oral administration of CV-11974 to conscious normotensive rats at 1 mg/kg resulted in long-lasting inhibition of the AII-induced pressor response. CV-11974 at 0.1-1 mg/kg i.v. reduced blood pressure dose-dependently in spontaneously hypertensive rats.

IT **150058-22-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and angiotensin II receptor antagonist activity of)

RN 150058-22-3 CAPLUS

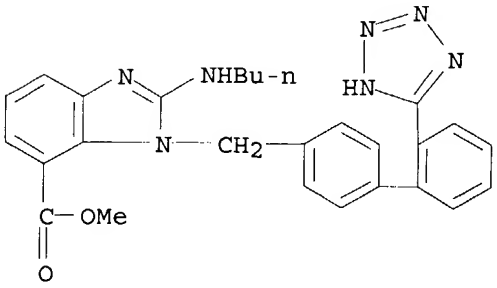
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylsulfinyl)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



IT **139481-96-2P 139481-99-5P 139482-05-6P**
150058-20-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and saponification of)

RN 139481-96-2 CAPLUS

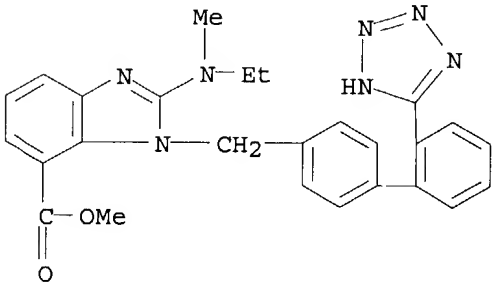
CN 1H-Benzimidazole-7-carboxylic acid, 2-(butylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



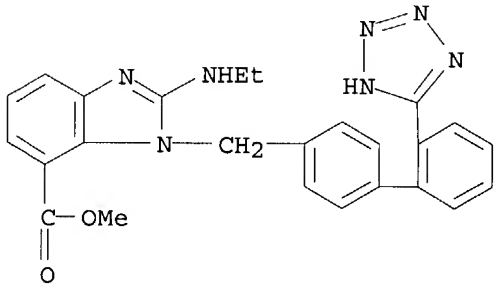
RN 139481-99-5 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylmethylamino)-1-[[2'-(1H-

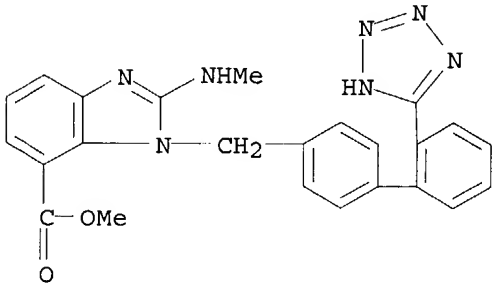
tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



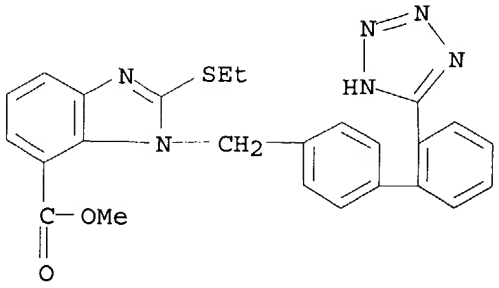
RN 139482-05-6 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



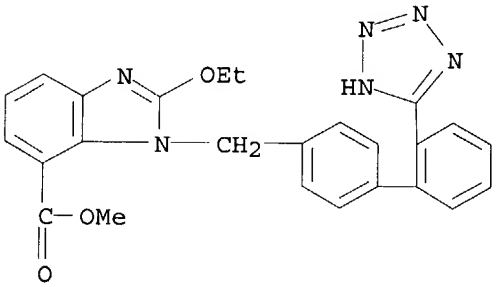
RN 150058-20-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(methylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



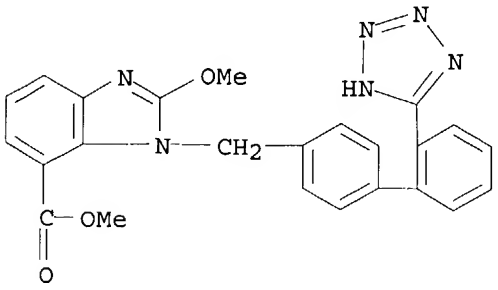
IT **150058-21-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, hydrolysis, and angiotensin II receptor antagonist activity of)
RN 150058-21-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylthio)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



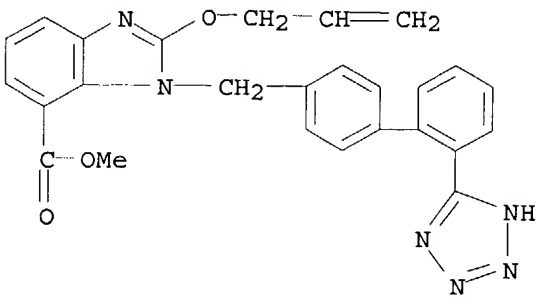
IT **139481-69-9P 139481-75-7P 139481-94-0P**
139481-95-1P 139482-06-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, saponification, and angiotensin II receptor antagonist activity of)
RN 139481-69-9 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



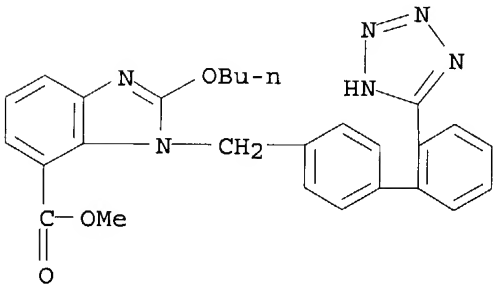
RN 139481-75-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



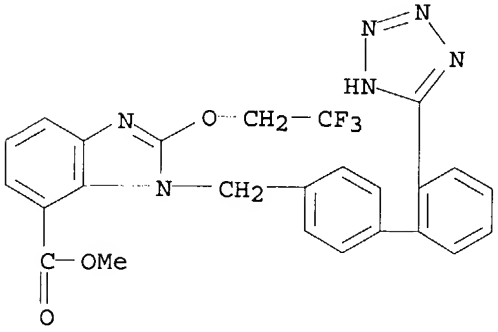
RN 139481-94-0 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(2-propenyloxy)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



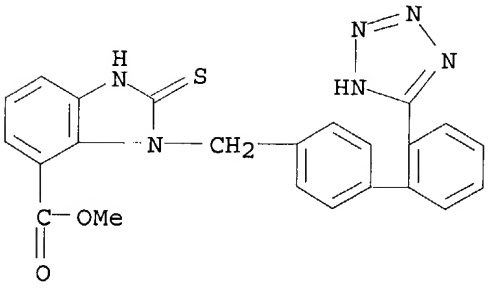
RN 139481-95-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-butoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-06-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)-, methyl ester (9CI) (CA INDEX NAME)



IT **150058-19-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, saponification, and methylation of)
RN 150058-19-8 CAPLUS
CN 1H-Benzimidazole-4-carboxylic acid, 2,3-dihydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-thioxo-, methyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:128924 CAPLUS
DOCUMENT NUMBER: 116:128924
TITLE: Preparation of benzimidazole derivatives as angiotensin II antagonists
INVENTOR(S): Naka, Takehiko; Nishikawa, Kohei; Kato, Takeshi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 70 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 459136	A1	19911204	EP 1991-106330	19910419
EP 459136	B1	19961227		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
IL 97882	A1	19961114	IL 1991-97882	19910416
US 5196444	A	19930323	US 1991-687238	19910418
EP 720982	A1	19960710	EP 1995-118796	19910419
EP 720982	B1	20021113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 146779	E	19970115	AT 1991-106330	19910419
ES 2095266	T3	19970216	ES 1991-106330	19910419
AT 227709	E	20021115	AT 1995-118796	19910419
ES 2181742	T3	20030301	ES 1995-118796	19910419
CA 2040955	AA	19911028	CA 1991-2040955	19910422
CA 2040955	C	19980203		
NO 9101586	A	19911028	NO 1991-1586	19910422
ZA 9102983	A	19920129	ZA 1991-2983	19910422
JP 04364171	A2	19921216	JP 1991-189614	19910422
JP 2514282	B2	19960710		
CA 2204290	C	20011218	CA 1991-2204290	19910422
CN 1055927	A	19911106	CN 1991-102569	19910423
CN 1048486	B	20000119		
AU 9175331	A1	19911121	AU 1991-75331	19910423
AU 647469	B2	19940324		
HU 57736	A2	19911230	HU 1991-1347	19910423
HU 213266	B	19970428		
RU 2052455	C1	19960120	RU 1991-4895495	19910423
PL 168958	B1	19960531	PL 1991-292174	19911025
PL 169116	B1	19960628	PL 1991-308620	19911025
PL 169451	B1	19960731	PL 1991-308621	19911025
PL 170324	B1	19961129	PL 1991-308619	19911025

CZ 289405	B6	20020116	CZ 1991-3239	19911025
SK 282473	B6	20020205	SK 1991-3239	19911025
LV 10258	B	19950420	LV 1992-567	19921230
US 5328919	A	19940712	US 1993-997703	19930105
LT 3246	B	19950425	LT 1993-438	19930319
US 5401764	A	19950328	US 1993-58739	19930510
US 5705517	A	19980106	US 1993-131667	19931005
JP 08099960	A2	19960416	JP 1995-220844	19950829
JP 2853611	B2	19990203		
CN 1147515	A	19970416	CN 1996-107765	19960523
CN 1058966	B	20001129		
US 5703110	A	19971230	US 1996-715100	19960917
NO 9700195	A	19970116	NO 1997-195	19970116
US 5962491	A	19991005	US 1997-924919	19970908
FI 9802761	A	19981221	FI 1998-2761	19981221
US 6004989	A	19991221	US 1999-280094	19990329
US 6232334	B1	20010515	US 1999-376494	19990818
US 2001047020	A1	20011129	US 2001-817231	20010327
FI 2001002172	A	20011109	FI 2001-2172	20011109
US 2002151723	A1	20021017	US 2002-46189	20020116
US 6608210	B2	20030819		
US 2004044223	A1	20040304	US 2003-612984	20030707

PRIORITY APPLN. INFO.:

JP 1990-113148	A	19900427
JP 1990-141942	A	19900530
JP 1990-208662	A	19900806
JP 1990-264579	A	19901001
JP 1990-413679	A	19901224
JP 1992-141942	A	19900530
US 1991-687238	A3	19910418
EP 1991-106330	A3	19910419
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FI 1991-1936	A3	19910422
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US 1993-997703	A3	19930105
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US 1993-131667	A3	19931005
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US 1999-280094	A3	19990329
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US 2001-817231	A3	20010327
US 2002-46189	A3	20020116

OTHER SOURCE(S): MARPAT 116:128924
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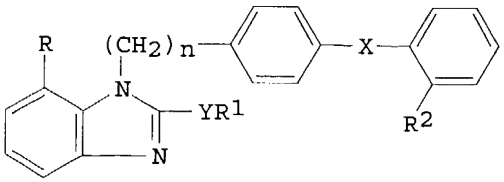

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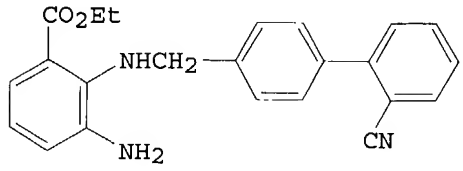


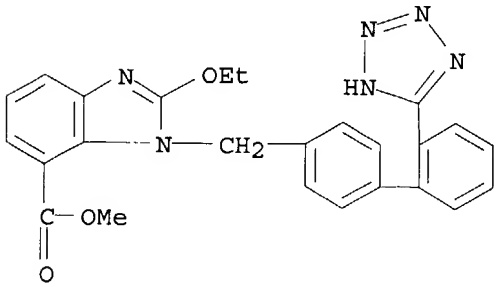
II

AB Benzimidazole derivs. [I; R = (esterified) CO2H, CONH2, a group capable of forming an anion; R1 = H, (substituted) hydrocarbyl; R2 = a group capable of forming an anion; X = bond, spacer of 1 or 2 atoms; Y = O, S(O)m (m = 0, 1, 2), NR4 = H, (substituted) alkyl; n = 1, 2], useful in treating hypertension, heart diseases, etc., are prepared HOAc was added to a solution of ester II in C(OMe)4 with stirring at 80° to give 90% I (R = CO2Et, YR1 = OMe, R2 = cyano, X = bond, n = 1). Also prepared were 58 addnl. I, which showed up to 96% inhibition of angiotensin II binding at 10-6M in a radioreceptor assay.

IT **139481-69-9P 139481-75-7P 139481-94-0P**
139481-95-1P 139481-96-2P 139481-99-5P
139482-05-6P 139482-06-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as angiotensin II antagonist)

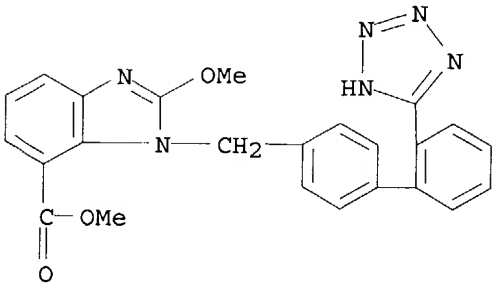
RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

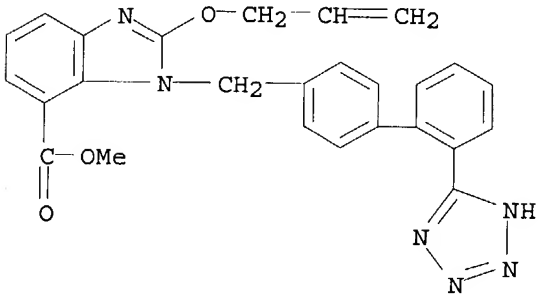


RN 139481-75-7 CAPLUS

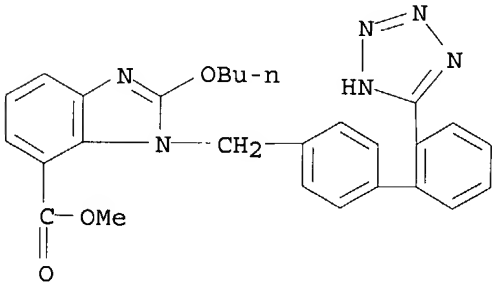
CN 1H-Benzimidazole-7-carboxylic acid, 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



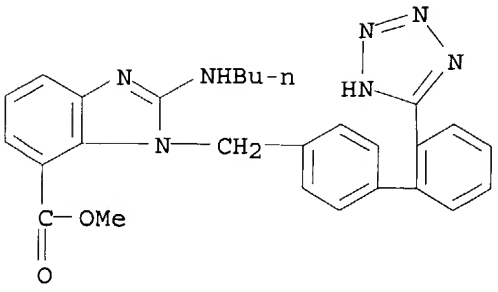
RN 139481-94-0 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(2-propenyloxy)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



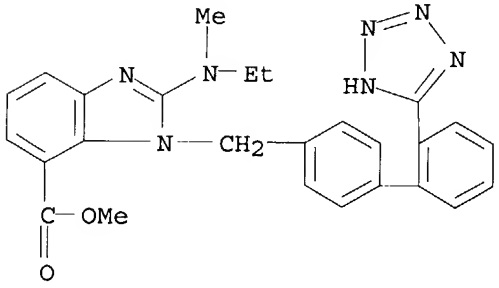
RN 139481-95-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-butoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



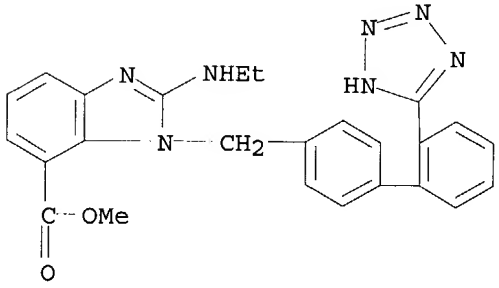
RN 139481-96-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(butylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



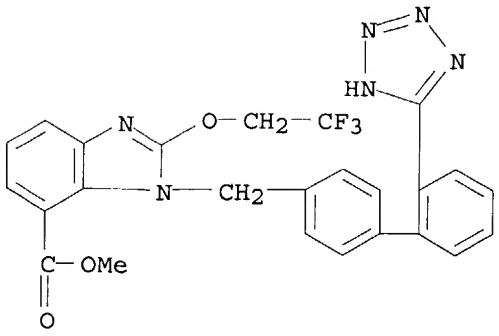
RN 139481-99-5 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylmethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-05-6 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-06-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)-, methyl ester (9CI) (CA INDEX NAME)



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L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:133265 CAPLUS
DOCUMENT NUMBER: 138:170242
TITLE: Preparation of crystals of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid and process for producing the same
INVENTOR(S): Hashimoto, Hideo; Maruyama, Hideaki
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003014112	A1	20030220	WO 2002-JP7861	20020801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1420016	A1	20040519	EP 2002-758782	20020801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2003113180	A2	20030418	JP 2002-225642	20020802

PRIORITY APPLN. INFO.: JP 2001-236802 A 20010803
WO 2002-JP7861 W 20020801

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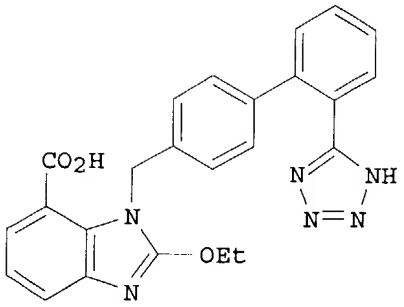


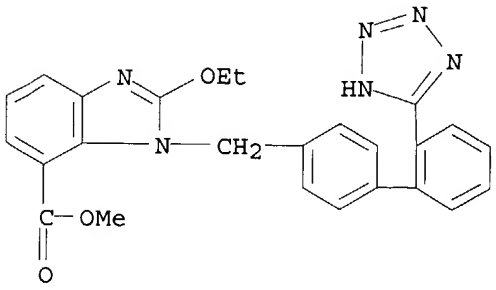
I

AB Disclosed is a process for producing crystals of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (I), characterized by dissolving or suspending the compound I or a salt thereof in a solvent comprising an aprotic polar solvent and crystallizing it. By the process, the impurities which are contained in the compound I or its salt and are difficult to remove, such as tin compds., analogs of the compound I, and a residual organic solvent, can be easily removed. Crystals of the compound I can be efficiently and easily mass-produced in high yield on an industrial scale. The compound I is useful as an angiotensin II inhibitor for the treatment of diseases induced by angiotensin II or a factor induced by angiotensin II, or diseases induced by angiotensin II receptor-mediated vascular contraction and proliferation and organ disorders, e.g. hypertension and heart diseases. Thus, 5.0 g I (preparation given), 6 mL THF, and 6 mL H2O were mixed, dissolved, stirred with 0.15 g activated charcoal for .apprx.30 min, filtered, followed by washing the charcoal with a mixture of THF and H2O (9:1) (10 mL), and the filtrate and the washing were combined, treated dropwsie with 87.5 mL H2O, and stirred for .apprx.1 h. The precipitated crystals were separated, washed with 20 mL THF/H2O (2:3), and dried to give 4.5 g I (90% yield) containing 0.08% ketone, 0.06% ester, 3,780 ppm THF, and ≤0.6 ppm Sn.

IT **139481-69-9P**, Methyl 1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis to free acid)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

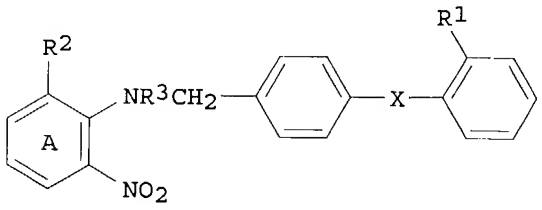


REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:779811 CAPLUS
DOCUMENT NUMBER: 130:53943
TITLE: Production of aminobenzene compounds with improved worker safety
INVENTOR(S): Hashimoto, Hideo; Hanaoka, Tadashi; Kato, Masayasu
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 31 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 881212	A1	19981202	EP 1998-109211	19980520
EP 881212	B1	20011031		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6177587	B1	20010123	US 1998-80456	19980519
AT 207884	E	20011115	AT 1998-109211	19980520
ES 2162367	T3	20011216	ES 1998-109211	19980520
CA 2238427	AA	19981126	CA 1998-2238427	19980525
CN 1203223	A	19981230	CN 1998-101894	19980525
JP 11043474	A2	19990216	JP 1998-142653	19980525
JP 3003030	B2	20000124		

PRIORITY APPLN. INFO.: JP 1997-134195 A 19970526
OTHER SOURCE(S): MARPAT 130:53943
GI



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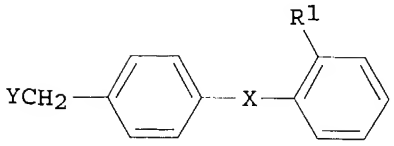

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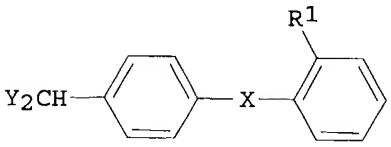
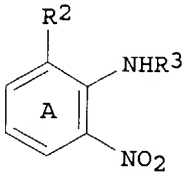


III



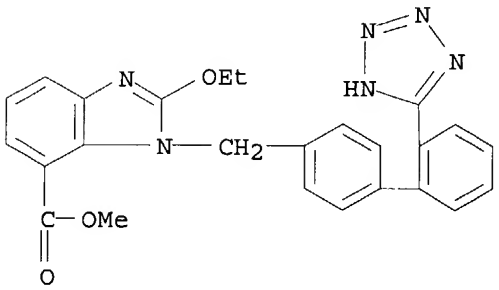
IV

AB Aminobenzene compds. I (R1, R2 are groups capable of forming an anion; R3 = acyl; X = bond, spacer of 1-2 atoms; A is a benzene ring which may have addnl. optional substituents) are prepared by reacting a mixture of a monohalogen compound II (Y is a halogen) and dihalogen compound III with an aminobenzene IV. The I are easily produced in in good yield in a completely airtight system, avoiding worker exposure to mutagenic II and salts thereof, and are useful as synthetic intermediates for the production of medicines.

IT **139481-69-9P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of; in production of aminobenzene compds. with improved worker safety)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:712908 CAPLUS
DOCUMENT NUMBER: 126:384
TITLE: Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres
AUTHOR(S): Kohara, Yasuhisa; Kubo, Keiji; Imamiya, Eiko; Wada, Takeo; Inada, Yoshiyuki; Naka, Takehiko
CORPORATE SOURCE: Pharmaceutical Research Divisions, Takeda Chemical Industries Ltd., Osaka, 532, Japan
SOURCE: Journal of Medicinal Chemistry (1996), 39(26), 5228-5235
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

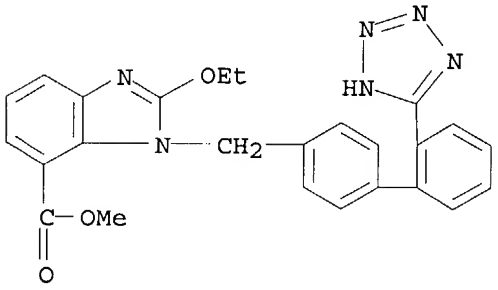
AB The design, synthesis, and biol. activity of benzimidazole-7-carboxylic acids bearing 5-oxo-1,2,4-oxadiazole, 5-oxo-1,2,4-thiadiazole, 5-thioxo-1,2,4-oxadiazole, and 2-oxo-1,2,3,5-oxathiadiazole rings are described. The compds. were evaluated for in vitro and in vivo angiotensin II (AII) receptor antagonistic activities. Most were found to have high affinity for the AT1 receptor (IC50 value, 10-6-10-7M) and to inhibit the AII-induced pressor response (more than 50% inhibition at 1 mg/kg po). The 5-oxo-1,2,4-oxadiazole, 5-oxo-1,2,4-thiadiazole, and 5-thioxo-1,2,4-oxadiazole derivs. showed stronger inhibitory effects than the corresponding tetrazole derivs., while their binding affinities were weaker. This might be ascribed to their improved bioavailability by

increased lipophilicity. This study showed that the 5-oxo-1,2,4-oxadiazole ring and its thio analog, the 5-oxo-1,2,4-thiadiazole ring, could be lipophilic bioisosteres for the tetrazole ring in nonpeptide AII receptor antagonists.

IT **139481-69-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and angiotensin II receptor antagonistic activities of benzimidazole derivs.)

RN 139481-69-9 CAPLUS

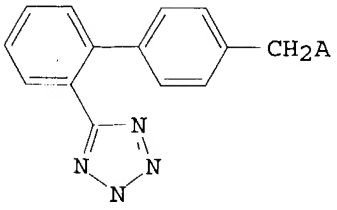
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:270821 CAPLUS
DOCUMENT NUMBER: 120:270821
TITLE: Tri-higher alkyl tin azide and its use
INVENTOR(S): Kato, Takeshi; Shida, Yasushi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 578125	A1	~~19940112~~	EP 1993-110458	19930630
EP 578125	B1	19980401		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5484955	A	19960116	US 1993-83697	19930629
AT 164584	E	19980415	AT 1993-110458	19930630
ES 2113975	T3	19980516	ES 1993-110458	19930630
CA 2099822	AA	19940107	CA 1993-2099822	19930705
CA 2099822	C	20031216		
JP 06073028	A2	19940315	JP 1993-166639	19930706
JP 2990566	B2	19991213		
JP 06073029	A2	19940315	JP 1993-166640	19930706
US 5599943	A	19970204	US 1995-519717	19950828

PRIORITY APPLN. INFO.: JP 1992-178484 A 19920706
US 1993-83697 A3 19930629
OTHER SOURCE(S): MARPAT 120:270821
GI



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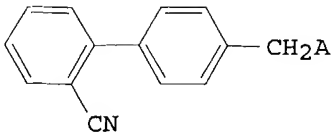


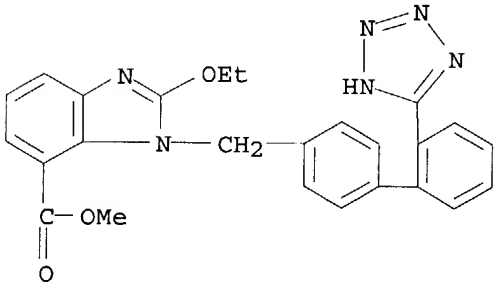
II

AB Disclosed are a compound of the formula (R)3SnN3, wherein R is a C7-18 alkyl, and a process for producing a tetrazolylbenzene compd.of formula I (A = H, phthalimido group) which comprises reacting a cyanobenzene compound, e.g., II with a (R)3SnN3. This process is useful for a safe and com. profitable production of the tetrazolylbenzene compound which is employed for producing a tetrazole derivative having a hypotensive action based on angiotensin II-antagonizing activity or a production intermediate thereof.

IT **139481-69-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 139481-69-9 CAPLUS

CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



L4 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1993:560184 CAPLUS

DOCUMENT NUMBER: 119:160184

TITLE: Nonpeptide angiotensin II receptor antagonists. Synthesis and biological activity of benzimidazolecarboxylic acids

AUTHOR(S): Kubo, Keiji; Kohara, Yasuhisa; Imamiya, Eiko; Sugiura, Yoshihiro; Inada, Yoshiyuki; Furukawa, Yoshiyasu; Nishikawa, Kohei; Naka, Takehiko

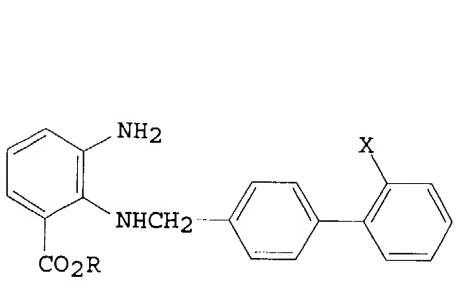
CORPORATE SOURCE: Pharm. Res. Div., Takeda Chem. Ind., Ltd., Osaka, 532, Japan

SOURCE: Journal of Medicinal Chemistry (1993), 36(15), 2182-95
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



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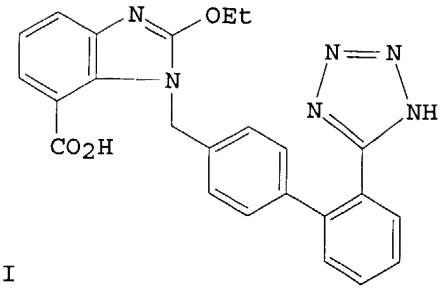


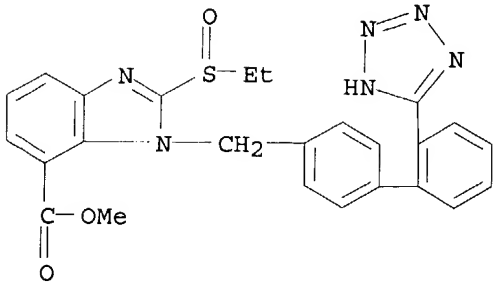
II

AB A series of 2-substituted-1-(biphenyl-4-ylmethyl)-1H-benzimidazole-7-carboxylic acids was prepared from the key intermediate 3-amino-2-[(biphenyl-4-ylmethyl)amino]benzoate I (R = Me, Et, X = CN, R = Me, X = CO2Me) in order to clarify the structure-activity relationships of various analogs of 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (CV-11194), a potent and long acting angiotensin II (AII) receptor antagonist. The AII antagonistic activity of the benzimidazoles was investigated by in vitro assays, which included an AII receptor binding assay and AII-induced vasocontraction assay, as well as by in vivo assays such as an AII-induced pressor response in rats. Most of the benzimidazoles showed high affinity for the AII receptor (IC50 value, 10-6-10-7 M) and inhibited the AII-induced pressor response at 1 or 3 mg/kg po, and the effects were more potent than those of CV-11194 and DuP753. The structure-activity relationship studies on the binding affinity and the inhibition of AII-induced pressor response suggested that straight chains of a certain length (e.g., ethoxy groups, Et groups) were the best as substituents at the 2-position and that their steric factors, lipophilicity, and electronic effects affected the potency of the AII antagonistic action. Both a carboxyl group at the 7-position and a tetrazole ring at the 2'-position were particularly important for potent and orally active AII antagonistic activity and a long-acting hypotensive effect. The representative compound, 2-ethoxy-1-[[2-(1H-tetrazol-5-yl)biphenyl]-4-ylmethyl]-1H-benzimidazole-7-carboxylic acid (CV-11974) (II), inhibited the specific binding of [125I]AII to bovine adrenal cortical membrane with an IC50 value of 1.1 + 10-7 M. The AII-induced contraction of rabbit aortic strips was antagonized by CV-11974 (IC50 value, 3.0 + 10-10 M). Oral administration of CV-11974 to conscious normotensive rats at 1 mg/kg resulted in long-lasting inhibition of the AII-induced pressor response. CV-11974 at 0.1-1 mg/kg i.v. reduced blood pressure dose-dependently in spontaneously hypertensive rats.

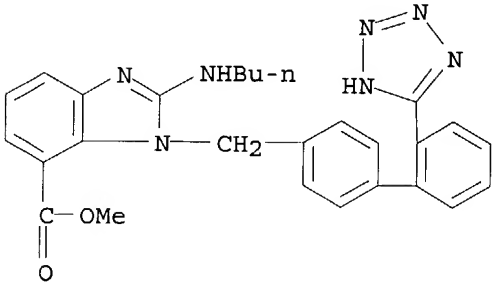
IT **150058-22-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and angiotensin II receptor antagonist activity of)

RN 150058-22-3 CAPLUS

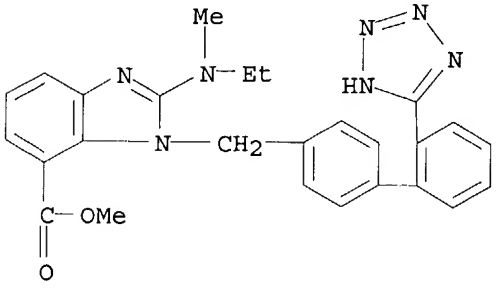
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylsulfinyl)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



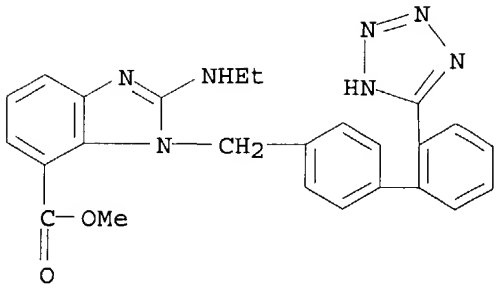
IT **139481-96-2P 139481-99-5P 139482-05-6P 150058-20-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and saponification of)
RN 139481-96-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(butylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



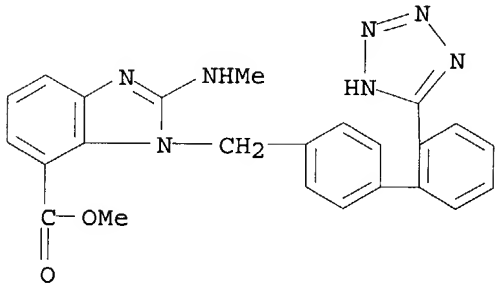
RN 139481-99-5 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylmethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



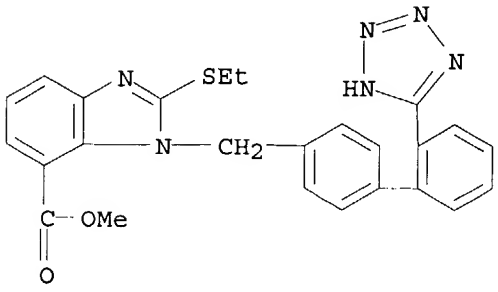
RN 139482-05-6 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 150058-20-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(methylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

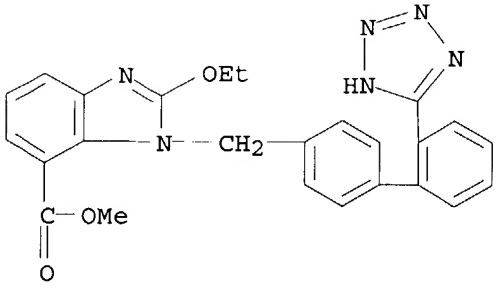


IT **150058-21-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, hydrolysis, and angiotensin II receptor antagonist activity of)
RN 150058-21-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylthio)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

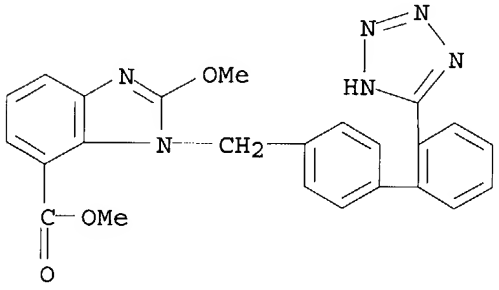


IT **139481-69-9P 139481-75-7P 139481-94-0P**
139481-95-1P 139482-06-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, saponification, and angiotensin II receptor antagonist activity of)
RN 139481-69-9 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-

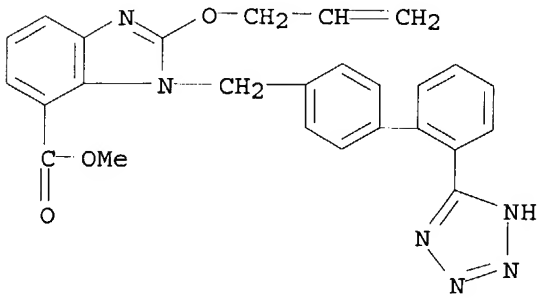
yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



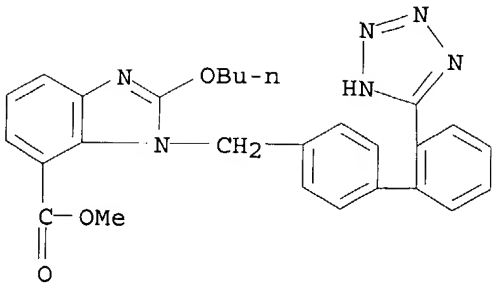
RN 139481-75-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



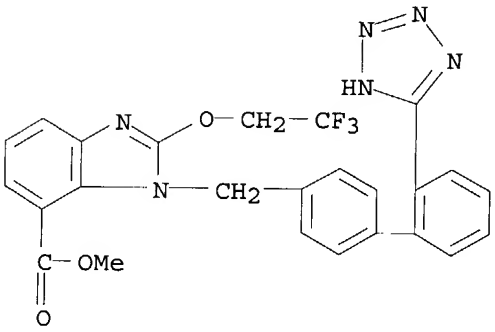
RN 139481-94-0 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(2-propenyloxy)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



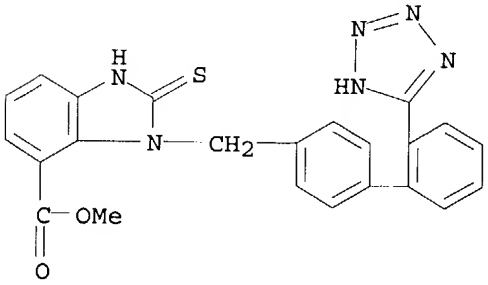
RN 139481-95-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-butoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-06-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)-, methyl ester (9CI) (CA INDEX NAME)



IT **150058-19-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, saponification, and methylation of)
RN 150058-19-8 CAPLUS
CN 1H-Benzimidazole-4-carboxylic acid, 2,3-dihydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-thioxo-, methyl ester (9CI) (CA INDEX NAME)



L4 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:128924 CAPLUS
DOCUMENT NUMBER: 116:128924
TITLE: Preparation of benzimidazole derivatives as

angiotensin II antagonists
INVENTOR(S): Naka, Takehiko; Nishikawa, Kohei; Kato, Takeshi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 70 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 459136	A1	19911204	EP 1991-106330	19910419
EP 459136	B1	19961227		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
IL 97882	A1	19961114	IL 1991-97882	19910416
US 5196444	A	19930323	US 1991-687238	19910418
EP 720982	A1	19960710	EP 1995-118796	19910419
EP 720982	B1	20021113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 146779	E	19970115	AT 1991-106330	19910419
ES 2095266	T3	19970216	ES 1991-106330	19910419
AT 227709	E	20021115	AT 1995-118796	19910419
ES 2181742	T3	20030301	ES 1995-118796	19910419
CA 2040955	AA	19911028	CA 1991-2040955	19910422
CA 2040955	C	19980203		
NO 9101586	A	19911028	NO 1991-1586	19910422
ZA 9102983	A	19920129	ZA 1991-2983	19910422
JP 04364171	A2	19921216	JP 1991-189614	19910422
JP 2514282	B2	19960710		
CA 2204290	C	20011218	CA 1991-2204290	19910422
CN 1055927	A	19911106	CN 1991-102569	19910423
CN 1048486	B	20000119		
AU 9175331	A1	19911121	AU 1991-75331	19910423
AU 647469	B2	19940324		
HU 57736	A2	19911230	HU 1991-1347	19910423
HU 213266	B	19970428		
RU 2052455	C1	19960120	RU 1991-4895495	19910423
PL 168958	B1	19960531	PL 1991-292174	19911025
PL 169116	B1	19960628	PL 1991-308620	19911025
PL 169451	B1	19960731	PL 1991-308621	19911025
PL 170324	B1	19961129	PL 1991-308619	19911025
CZ 289405	B6	20020116	CZ 1991-3239	19911025
SK 282473	B6	20020205	SK 1991-3239	19911025
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US 5328919	A	19940712	US 1993-997703	19930105
LT 3246	B	19950425	LT 1993-438	19930319
US 5401764	A	19950328	US 1993-58739	19930510
US 5705517	A	19980106	US 1993-131667	19931005
JP 08099960	A2	19960416	JP 1995-220844	19950829
JP 2853611	B2	19990203		
CN 1147515	A	19970416	CN 1996-107765	19960523
CN 1058966	B	20001129		
US 5703110	A	19971230	US 1996-715100	19960917
NO 9700195	A	19970116	NO 1997-195	19970116
US 5962491	A	19991005	US 1997-924919	19970908
FI 9802761	A	19981221	FI 1998-2761	19981221
US 6004989	A	19991221	US 1999-280094	19990329
US 6232334	B1	20010515	US 1999-376494	19990818
US 2001047020	A1	20011129	US 2001-817231	20010327

FI 2001002172	A	20011109	FI 2001-2172	20011109
US 2002151723	A1	20021017	US 2002-46189	20020116
US 6608210	B2	20030819		
US 2004044223	A1	20040304	US 2003-612984	20030707

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JP 1990-113148	A	19900427
JP 1990-141942	A	19900530
JP 1990-208662	A	19900806
JP 1990-264579	A	19901001
JP 1990-413679	A	19901224
JP 1992-141942	A	19900530
US 1991-687238	A3	19910418
EP 1991-106330	A3	19910419
CA 1991-2040955	A3	19910422
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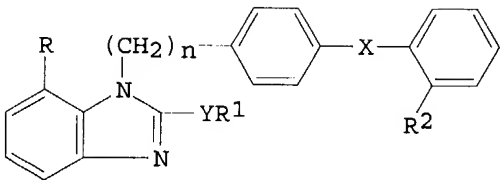
OTHER SOURCE(S): MARPAT 116:128924

GI



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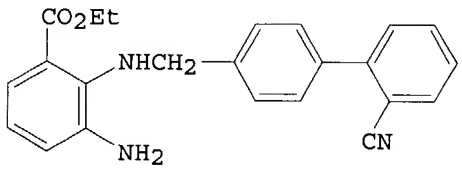


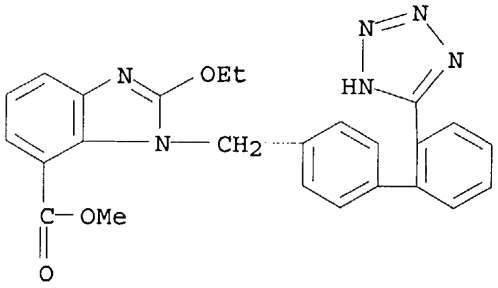
II

AB Benzimidazole derivs. [I; R = (esterified) CO2H, CONH2, a group capable of forming an anion; R1 = H, (substituted) hydrocarbyl; R2 = a group capable of forming an anion; X = bond, spacer of 1 or 2 atoms; Y = O, S(O)m (m = 0, 1, 2), NR4 = H, (substituted) alkyl; n = 1, 2], useful in treating hypertension, heart diseases, etc., are prepared HOAc was added to a solution of ester II in C(OMe)4 with stirring at 80° to give 90% I (R = CO2Et, YR1 = OMe, R2 = cyano, X = bond, n = 1). Also prepared were 58 addnl. I, which showed up to 96% inhibition of angiotensin II binding at 10-6M in a radioreceptor assay.

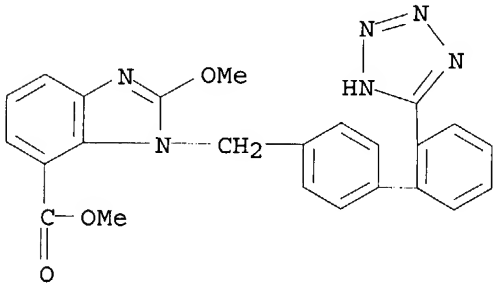
IT **139481-69-9P 139481-75-7P 139481-94-0P**
139481-95-1P 139481-96-2P 139481-99-5P
139482-05-6P 139482-06-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as angiotensin II antagonist)

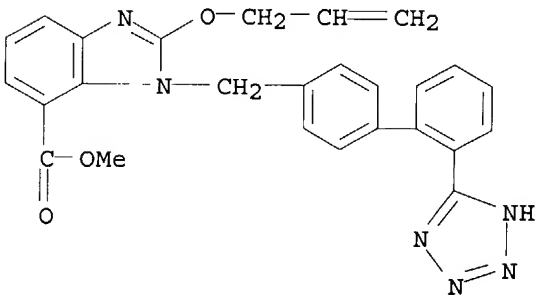
RN 139481-69-9 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



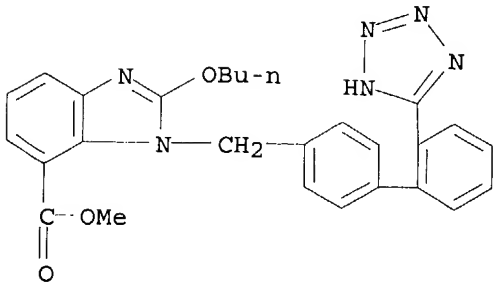
RN 139481-75-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-methoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



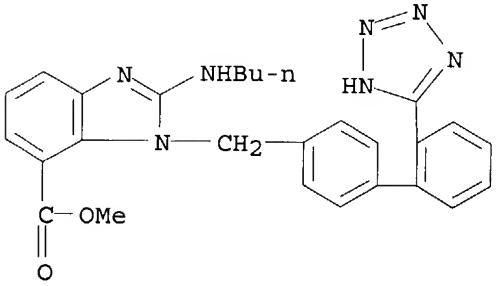
RN 139481-94-0 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(2-propenyloxy)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



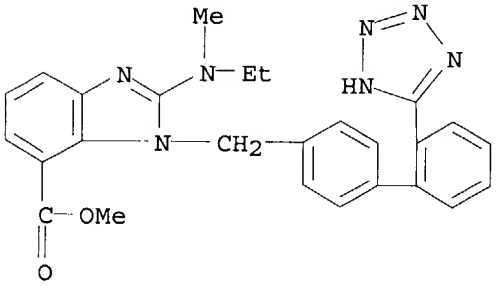
RN 139481-95-1 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-butoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



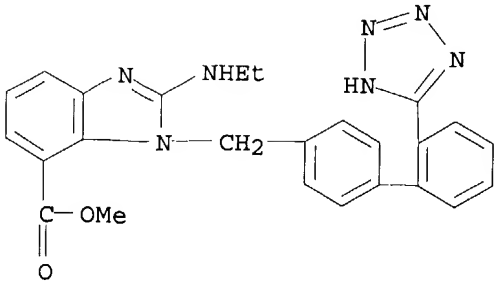
RN 139481-96-2 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(butylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



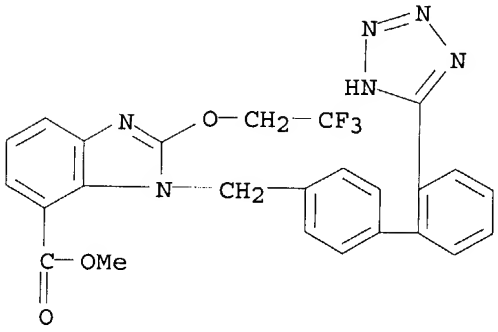
RN 139481-99-5 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylmethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-05-6 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 2-(ethylamino)-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 139482-06-7 CAPLUS
CN 1H-Benzimidazole-7-carboxylic acid, 1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2-(2,2,2-trifluoroethoxy)-, methyl ester (9CI) (CA INDEX NAME)



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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	55.89	211.73
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-7.62	-7.62

STN INTERNATIONAL LOGOFF AT 13:09:47 ON 17 JUN 2004